AR201-12680a

Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy-

CAS No. 2530-83-8

Test Plan
Reduced Testing Rationale
Robust Summaries

July 20, 2000

Submitted to EPA under the HPV Challenge Program by:

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Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy-[1]
Test Plan

CAS No. 2530-83-8

Silicones Environmental, Health and Safety Council
July 20, 2000

Chemical	Physical-Chemical				
	Melting Point	Boiling Point	Vapor Pressure	Partition Coefficient	Water Solubility
2530-83-8 Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy-[1]	NR[2]	A	A	NA[3]	NA[3]

Chemical	Environmental Fate			
	Photo-degradation	Stability in Water	Transport/ Distribution	Biodegradation
2530-83-8 Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy-[1]	NA[3]	Test	NA[3]	A

Chemical	Ecotoxicity		
	Acute Toxicity to Fish	Acute Toxicity to Aquatic Plants (e.g., Algae)	Acute Toxicity to Aquatic Invertebrates (e.g., Daphnia)
2530-83-8 Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy-[1]	A	A	A

Chemical	Toxicity					
	Acute Toxicity	Genetic Toxicity *In Vitro*	Genetic Toxicity *In Vivo*	Repeat Dose Toxicity	Repro-ductive Toxicity	Develop-mental Toxicity
2530-83-8 Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy-[1]	A	A	A	A[4]	NA[3]	A[4]

[1] Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy- (CAS No. 2530-83-8) is also known, and will be referred to, as 3-(Trimethoxysilyl)propyl glycidol ether (TMSPGE) or 3-Glycidoxypropyltrimethoxysilane.

[2] Endpoint is not required because the melting point for this liquid is less 0°C. (a) Melting point <-70°C. Material Safety Data Sheet. CAS No. 2530-83-8. Union Carbide Chemicals and Plastics Company, Inc. Effective date 21 February 1991.

[3] Endpoints are not applicable because the chemical is hydrolytically unstable.

[4] As our experience and knowledge associated with the issues surrounding the testing of TMSPGE increased, it has become apparent that it is not stable by the oral route. Specifically, TMSPGE readily hydrolyzes to methanol and silanols (Note: methanol is included in the EPA HPV Challenge Program and the ICCA Global

Initiative on HPV Chemicals). pH has a significant effect on the rate of hydrolysis, and at pH 4, the hydrolysis is complete within 2.5 minutes. Slight changes in pH affect the rate of hydrolysis, which may result in administration of differing forms of the test article with each dosing. The hydrolysis rate is susceptible to the presence of trace acid and/or base. The lack of clinical signs of toxicity following acute or repeated dosing is likely related to the hydrolysis of TMSPGE and subsequent polymerization of the hydrolysis products, and thus, the lack of bioavailability.

Legend	
Symbol	**Description**
R	Endpoint requirement fulfilled using category approach, SAR
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties
O	Other

Date Work Plan Available for Comment: (Q3, 2000)

Date Work Plan Complete: (quarter, year)

Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy-[1] Reduced Testing Rationale

(Difficult-to-Test Substance)
CAS No. 2530-83-8

Silicones Environmental, Health and Safety Council
July 20, 2000

Introduction

EPA has recognized that some chemicals in the HPV Challenge Program are difficult to test for a number of reasons for one or more endpoints. Sponsors are encouraged to follow appropriate SIDS guidance, where available, and develop a rational test plan with the necessary alternative test battery.

Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy- (CAS No. 2530-83-8), also known and herein referred to as 3-(trimethoxysilyl)propyl glycidol ether (TMSPGE), is listed as an HPV Challenge Program chemical. In this document, the Silicones Environmental, Health and Safety Council (SEHSC) reviews the reactive nature of TMSPGE, the exposure potential and manufacturing, and use of this glycidol ether to support its proposed difficult-to-test status and associated reduced testing rationale.

TMSPGE is a highly reactive chemical and is subject to rapid hydrolysis. At pH 4, TMSPGE is completely hydrolyzed in 2.5 minutes. The calculated half-lives for hydrolysis at various pH values are given in Table 1.[2]

Table 1. The calculated half-lives for hydrolysis of TMSPGE at 25 °C at various pH values.

pH	3	4	5	6	7	8	9	11
Half-life	3.0	30	5.0	49	4.0	45	4.6	2.7
Time unit	second	second	minute	minute	hour	minute	minute	second

[1] Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy- (CAS No. 2530-83-8) is also known, and will be referred to, as 3-(trimethoxysilyl)propyl glycidol ether (TMSPGE) or 3-Glycidoxypropyltrimethoxysilane.

[2] Pohl, E.R. and F.D. Osterholtz. 1985. Kinetics and mechanism of aqueous hydrolysis and condensation of alkyltrialkoxysilanes. *Polym. Sci. Technol.* 27:157-170.

These data will be confirmed by additional hydrolysis studies to be conducted as indicated in the test plan for this substance. Preliminary results indicate that the hydrolysis rate is susceptible to any traces of base and may be dependent on the concentration of buffer.

In analyzing the adequacy of the existing data, we have conducted a thoughtful, qualitative analysis, and have concluded that there are sufficient data, given the totality of what is known about this chemical, including human experience, that certain endpoints need not be tested. Note that, throughout the development of the test plan, we have incorporated consideration of animal welfare concerns and scientific principles.

Three technical factors have been identified during the conduct of repeated toxicity testing that makes HPV toxicological testing infeasible and inappropriate. These factors are (1) the polymerization of the test article in the stomach following oral exposure, (2) the necrotizing effect of the test article following dermal exposure, and (3) the lack of exposure via inhalation based on a very low saturated vapor concentration [12 parts per million (ppm)]. Furthermore, as stated in EPA's Part 870 Health Effects Test Guidelines[3], additional factors related to typical exposures in humans further limit the choice of route of administration. That is, *"The choice of the route of administration depends upon the physical and chemical characteristics of the test substance and the form typifying exposures in humans."* Systemic effects via inhalation are unlikely since hydrolysis occurs when TMSPGE contacts moist air in the environment or the lung if released during use. Moreover, as TMSPGE hydrolyzes, its saturated vapor concentration at ambient temperatures falls below 12 ppm, reducing the potential for inhalation exposure to any residual TMSPGE. TMSPGE hydrolysis results in highly cross-liked, high molecular weight polymers, which further reduces the potential for exposure. The oral route of exposure is impracticable not only because ingestion is not intended by humans, but also because the test article rapidly hydrolyzes and polymerizes under stomach pH conditions. The hydrolysis and polymerization half-lives are so short that the absorption of the test article would be insufficient due to polymerization of the hydrolyzed test article in the stomach. The doses of TMSPGE that would be selected for dermal exposures are expected to be so low as to be meaningless. Furthermore, hydrolysis after application on, or contact with, the skin, respectively, is very likely to occur. This results in the formation of high molecular weight polymers that, due to their size, are not capable of penetrating the skin barrier such that systemic bioavailability is excluded.

Background Information: TMSPGE Exposure Potential, Manufacturing and Commercial Applications

The number of individuals likely to be exposed to TMSPGE is small and the potential levels of TMSPGE to which these individuals may be exposed are extremely low, as explained below.

Exposure During the Manufacture of TMSPGE

The physical and chemical properties of TMSPGE minimize the potential for exposure to this substance during its manufacture. Because TMSPGE has a low vapor pressure (the saturated vapor concentration at ambient temperatures is approximately 12 ppm), there is little potential for inhalation exposure.

[3] http://www.epa.gov/docs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/

Monitoring studies of manufacturing workers and manufacturing areas where potential exposure would be greatest (i.e., filling and pouring operations) confirm that only low concentrations (time weighted average (TWA) of 0.63 ppm) of TMSPGE are present in the workplace atmosphere. The likelihood of forming aerosols is very low and would occur only if improper handling procedures are used.

TMSPGE is a moisture-reactive material that hydrolyzes rapidly (half-life of < 3 seconds to about 4 hours, depending on the aqueous solution pH and concentration of buffer). In the unlikely event of an accidental spill, TMSPGE could enter the environment through evaporation (limited by the very low saturated vapor concentration) or through direct contamination of surfaces, soil and surface waters. TMSPGE will react with the humidity in the air, moisture in the soil, or directly with the water of streams, lakes, and rivers. The rate of hydrolysis will depend upon the nature of the spill. If TMSPGE is in contact with large amounts of liquid water (either surface water or cleaning solutions), hydrolysis will occur very rapidly (minutes or hours). However, if TMSPGE is only in contact with low humidity air, hydrolysis can take considerably longer. Moreover, as TMSPGE hydrolyzes, its saturated vapor concentration at ambient temperatures falls to below 12 ppm, reducing the potential for inhalation exposure to any residual TMSPGE. Hydrolysis of TMSPGE results in highly cross-linked, high molecular weight polymers, further reducing the potential for exposure.

The number of workers that may be exposed to TMSPGE during its manufacture or handling is small. Given its chemical and physical properties, manufacturing and processing of TMSPGE occurs in enclosed equipment. Thus, the only workers that may be potentially exposed to TMSPGE are those who transfer materials from reaction vessels to shipping containers or who are exposed to the material during cleaning operations. As indicated previously, TMSPGE rapidly hydrolyzes and its saturated vapor concentration at ambient temperatures falls to below 12 ppm, reducing the potential for inhalation exposure to any residual TMSPGE.

Exposure to Workers During End-Use Applications

Worker exposure to TMSPGE is low during its use in applications. In many of its applications, TMSPGE is only a small component of the formulation or article and TMSPGE is chemically altered during use by hydrolysis, condensation with surfaces, or oligomerization. The dilution and reactions of TMSPGE reduce its bioavailability and apply with equal validity to all of the end-use applications of this material.

- **Component in Adhesives and Sealants**

TMSPGE is used most frequently in minor proportions as an adhesion promoter, coupling agent, or cross linker in adhesives, sealants, and encapsulants. Regardless of the particular adhesive or sealant with which it is mixed, TMSPGE is essentially never used at concentrations higher than ten percent. A level of one to two percent by weight is a commonly recommended as a "starting-point" in many formulations.

Although the precise function of TMSPGE varies based on the sealant or adhesive to which it is added, it usually becomes immobilized during use due to attachment to minerals or polymers in the adhesive or sealant. In silicone sealants, much of the TMSPGE reacts with hydroxyl groups on silanol end-capped silicone polymers, with hydroxyl on the surface of silica reinforcing fillers, or with trace water introduced on mineral filler surfaces. In instances where TMSPGE is used as an additive to improve the

adhesion of water-based or latex caulks and sealants, TMSPGE is polymerized and immobilized during the formulation process by reacting with water and mineral surfaces that are present in these products.

TMSPGE is sometimes used in solvent-based or 100 percent actives sealants, adhesives, and encapsulants. In these adhesive applications, TMSPGE becomes partially immobilized by reaction with the mineral fillers during the manufacturing process and reacts completely with the organic polymer during the curing process. Thus, when acting as a "coupling agent" or an "adhesion promoter" with any of the above adhesives or sealants, TMSPGE becomes covalently bonded to very high molecular weight polymers and minerals. This bonding to a high molecular weight material greatly reduces potential exposures.

- **Component of Coatings on Glass Fibers**

Another major application for TMSPGE is as a raw material in the manufacture of reinforcing glass fibers. During its use, TMSPGE is deliberately converted to the silanol form by hydrolyzing it in acidified water at concentrations usually below twenty percent by weight and typically between five and ten percent by weight. After the hydrolysis reaction is complete, the aqueous solutions of TMSPGE are further diluted with water and possibly other ingredients, such as emulsions of organic polymers, lubricants, surfactants, wetting agent, and other processing aids.

During application of these solutions, called sizes or finishes, to the glass fibers, there exists a potential for worker exposure to the hydrolysis products of TMSPGE. However, after the fibers are dried, the worker exposure is diminished greatly because these silanols are bonded directly to the glass fibers. This immobilization and chemical reactivity eliminates further end-user exposure to TMSPGE or its hydrolysis products. The final end-user takes these fibers and mixes them with organic resins to make composites.

- **Component of Foundry Additives**

Less than five percent of the production volume of TMSPGE is consumed as an additive to a foundry resin. In this use, a resin producer blends a phenolic or furan resin (polymer), which contains some water, with a small quantity of TMSPGE, typically between 0.01 and 0.1 percent. As the TMSPGE is blended, it hydrolyzes to silanol and oligomer forms because there is water in the resin. Moreover, TMSPGE reacts with the resin during curing reactions. Therefore, potential exposure to unreacted TMSPGE is minimal.

Exposure to General Population

SEHSC is unaware of any consumer use of this substance, and there is no exposure to the general population. Exposure of the public or the environment to these materials is possible only from accidental releases and would be of a short duration. Exposure via inhalation following such releases is unlikely based on a low saturated vapor concentration (12 ppm). As TMSPGE hydrolyzes, its saturated vapor concentration at ambient temperatures falls to below 12 ppm, further reducing the potential for inhalation exposure to any residual TMSPGE.

Matrix of SIDS Endpoints

In order to construct a matrix of SIDS endpoints for TMSPGE, the data on physicochemical properties, environmental fate and effects, and health effects must be collected and evaluated for adequacy. The

results of these activities are presented in Table 2, which provides a matrix of available and adequate data on TMSPGE.

Table 2

Matrix of Available and Adequate Data on TMSPGE	
Test ***Physicochemical Properties***	
Melting Point	√[4]
Vapor Pressure	√
Boiling Point	√
Partition Coefficient	-
Water Solubility	-
Hydrolysis	√
Photodegradation	-
Biodegradation	√
Environmental Transport	-
Test ***Ecotoxicity***	
Acute Fish	√
Acute Daphnid	√
Algae	√
Terrestrial	NA
Test ***Heath Effects***	
Acute Oral	√
Acute Inhalation	√
Acute Dermal	-
Repeated Dose	√[5]
Genotoxicity (*in vitro* -bacteria)	√
Genotoxicity (*in vitro* - nonbacterial)	√
Genotoxicity (*in vivo*)	√
Repro/Developmental	√[5]
(√) = Data available and considered adequate; (NA) = Not applicable due to chemical/physical properties; (-) No data available, or data considered inadequate	

[4] Melting Point <-70°C. Material Safety Data Sheet. CAS No. 2530-83-8. Union Carbide Chemicals and Plastics Company, Inc. Effective date 21 February 1991.

[5] As our experience and knowledge associated with the issues surrounding the testing of TMSPGE increased, it has become apparent that it is not stable by the oral route. A non-GLP study was conducted to examine the fate of TMSPGE following oral (gavage) exposure. This study showed that little or no absorption of test article appeared to have occurred. The lack of clinical signs of toxicity following acute or repeated dosing is likely related to the hydrolysis of TMSPGE and subsequent polymerization of the hydrolysis products, and thus, the lack of bioavailability. The recognition of the instability of TMSPGE precludes future testing of this material via the oral route.

Reduced Testing Rationale

EPA has recognized that some chemicals in the HPV Challenge Program are difficult to test for a number of reasons for one or more endpoints. Sponsors are encouraged to follow appropriate SIDS guidance, where available, and develop a rational test plan with the necessary alternative test battery.

TMSPGE is a highly reactive chemical and is subject to rapid hydrolysis in the presence of moisture. At pH 4, TMSPGE is hydrolyzed completely in 2.5 minutes; at pH 11 or 3, the half-life is about 3 seconds, and at pH 9 or 5, the half-life is about 5 minutes.[6] Slight variations in pH (for example, at pH 7 vs. 7.2) result in a change in the rate of hydrolysis; furthermore, the hydrolysis rate is susceptible to any traces of base and may be dependent on buffer concentration. This material is extremely difficult to handle during the conduct of toxicological or environmental testing. Exposure of the public or the environment to these materials is possible only from accidental releases and would be of a short duration. TMSPGE hydrolyzes rapidly to form silanols and methanol. These silanol solutions can form highly cross-linked, high molecular weight polymers when dried. These polymers are not biologically available due to their high molecular weight. Methanol, a byproduct of the hydrolysis reaction, is included separately under EPA's HPV Challenge Program and the ICCA Global Initiative on HPV Chemicals.

Concentrated solutions of silanols that are formed upon hydrolysis of TMSPGE will condense to oligomers or polymers. Many of these oligomers and polymers are insoluble in an aqueous solution and will precipitate out. In contrast to soluble polymers from other silanes, the polymers from TMSPGE (if the epoxy ring does not open) have limited water solubility. TMSPGE will form silanetriol, dimers, trimers, and oligomers. Viscosity and solubility of gastric solutions of TMSPGE will depend on the degree of condensation, number of silanol groups remaining, and the degree of epoxy ring opening. Epoxy rings react in acidic water to form diols, but the rate of ring-opening is much slower than the rate of silane hydrolysis. The diol form of TMSPGE has higher water solubility.

Infeasibility of Health and Environmental Testing of TMSPGE

Toxicology testing requires exposure to animals in a moisture-containing environment. For example, in inhalation testing, ambient air contains a significant level of moisture (generally 30-70%). In aquatic toxicity tests, the test environment is water-based. In these and other testing situations, TMSPGE will hydrolyze to form methanol and silanols. As stated previously, the EPA HPV Challenge Program and the ICCA Global Initiative on HPV Chemicals separately includes methanol.

In analyzing the adequacy of the existing data, we have conducted a thoughtful, qualitative analysis, and have concluded that there are sufficient data, given the totality of what is known about this chemical, including human experience, that certain endpoints need not be tested. Note that, throughout the development of the test plan, we have incorporated consideration of animal welfare concerns and scientific principles. On this basis, an alternative test battery is planned.

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[6] Pohl, E.R. and F.D. Osterholtz. 1985. Kinetics and mechanism of aqueous hydrolysis and condensation of alkyltrialkoxysilanes. *Polym. Sci. Technol.* 27:157-170.

Detailed studies will be conducted to evaluate the hydrolysis kinetics and rate of degradation. However, because the material is known to be hydrolytically unstable and rapidly generates methanol when added to water, endpoints such as octanol/water partition coefficient and water solubility are not appropriate, and will not be determined. Similarly, environmental fate properties, which are not appropriate due to the nature of the test article, include photodegradation and transport/distribution modeling. Biodegradation studies suggest that about 37 percent of the material is degraded after 28 days. However, these results reflect the degradation of methanol and not the parent material. Aquatic toxicity testing indicates that TMSPGE is practically non-toxic (EC_{50} > 100 ppm) to fish, invertebrates, and algae.

A technical infeasibility has been identified with the conduct of repeated dose mammalian toxicity testing due to (1) the polymerization of the test article in the stomach following oral exposure, (2) the irritating nature of the test article following dermal exposure, and (3) the lack of exposure via inhalation based on a very low vapor pressure (12 ppm). Details describing the issues associated with the use of each of these exposure routes follow.

- **Oral Exposure**

Ingestion of TMSPGE is not an intended route of exposure for humans. As stated in EPA's Part 870 Health Effects Test Guidelines,[7] *"The choice of the route of administration depends upon the physical and chemical characteristics of the test substance and the form typifying exposures in humans."* Further, as described previously in this document, TMSPGE readily hydrolyzes to methanol and silanols. pH has a significant effect on the rate of hydrolysis, and at pH 4, the hydrolysis is complete within 2.5 minutes. Slight changes in pH also affect the rate of hydrolysis, which may result in exposure to differing forms of the test article with each administration. Finally, the hydrolysis rate is susceptible to the presence of even traces of base and may be dependent on buffer concentration.

A non-GLP study was conducted to examine the fate of TMSPGE following gavage. Five fasted female Sprague-Dawley rats were dosed with 2000 mg/kg TMSPGE mixed with activate charcoal as a tracer. After 20 or 30 minutes the animals were sacrificed, and the stomachs and gastrointestinal tracts examined for presence of test article. The study was also repeated in the absence of the activated charcoal tracer. In all cases, the test article was found in the stomach contents or in the upper gastrointestinal tract, and was observed to have the consistency of thick mucous. In cases where the stomach contents included food, small waxy particles of test article were observed. Both the thick mucous and waxy particle forms of the test article observed in the stomach and upper gastrointestinal tract support the rapid polymerization of TMSPGE under oral (gavage) conditions, as the test article exists as a clear, water-like liquid. In either case, little or no absorption of test article appeared to have occurred. In contrast, there was no liquid present in the stomachs of animals gavaged with an equivalent dose of water and sacrificed after 30 minutes.[8]

The low order of acute or repeated dose toxicity associated with TMSPGE is attributed to the lack of bioavailability. The conduct of additional studies will not contribute to an additional understanding of the potential health effects of this material, and it is unnecessary to proceed with further testing involving animals. Additional information obtained through the repeated oral testing of TMSPGE would not be useful or relevant.

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[7] http://www.epa.gov/docs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/

[8] WIL Research. July 2000. Single Dose Study in Albino Rats. Study No. WIL-401001.

- **Dermal Exposure**

Application of small amounts of TMSPGE (0.01 mL) to the clipped skin of the rabbit belly uncovered for 24 hours resulted in moderate to marked capillary injection. In a preliminary study of the irritant potential from recurrent applications of TMSPGE to the skin of mice, a maximum concentration of TMSPGE of 25 percent in acetone was selected in order to avoid significant primary skin irritation over the lifetime of the animals.

A human patch test was conducted to determine whether TMSPGE was capable of causing skin irritation in humans under controlled conditions, and if so, to classify the material as a "primary" irritant on the basis of the observed clinical response. TMSPGE was applied to the infrascapular area of the back, under an occlusive patch at concentrations of 100, 75, 50, 25, 10, and 1% (in methanol) for a period of 48-hours. TMSPGE was very irritating under the conditions employed in this study, with initial reactions (after 48 and 74 hours) characterized by redness, scaling and crusting, edema, and hyperpigmentation. Definite irritation was observed at 100, 75, 50, and 25% concentrations, while the irritation was not considered clinically significant at concentrations of 1 and 10%.

As stated in EPA and OECD test guidance, the highest dose selected in a repeated dose study should result in toxic effects. The dermal studies conducted with TMSPGE suggest that a sufficiently high dose of TMSPGE could not be applied during a repeated dose study without significant skin irritation.

The doses of TMSPGE that would be selected for dermal exposures are expected to be so low as to be meaningless. Furthermore, hydrolysis after application on, or contact with, the skin, respectively, is very likely to occur. This results in the formation of high molecular weight polymers that, due to their size, are not capable of penetrating the skin barrier such at systemic bioavailability is excluded. The conduct of repeated dose dermal studies will not contribute to an additional understanding of the potential health effects of this material, and would serve as an unnecessary use of laboratory animals.

- **Inhalation Exposure**

The physical and chemical properties of TMSPGE minimize the potential for exposure to this substance during its manufacture. Because TMSPGE has a low vapor pressure (the saturated vapor concentration at ambient temperatures is approximately 12 ppm), there is little potential for inhalation exposure. As TMSPGE hydrolyzes, its saturated vapor concentration at ambient temperatures falls to below 12 ppm, further reducing the potential for inhalation exposure to any residual TMSPGE.

Monitoring studies of manufacturing workers and manufacturing areas where potential exposure would be greatest, i.e., filling and pouring operations, confirm that only low concentrations (TWA of 0.63 ppm) of TMSPGE are present in the workplace atmosphere. Exposure of the public or the environment to these materials is possible only from accidental releases and would be of a short duration.

Repeated dose studies, including additional reproductive and developmental endpoints, will not be included in the HPV test plan for TMSPGE because of the rapid hydrolysis following contact with moisture, and the production of biologically unavailable high molecular weight polymer. The conduct of inhalation toxicity studies will not contribute to an additional understanding of the potential health effects of this material, and would serve as an unnecessary use of laboratory animals.

AR201-12680b

Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy-[1] Robust Summaries CAS No. 2530-83-8

Silicones Environmental, Health and Safety Council
July 20, 2000

Contents

[1] Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy- (CAS No. 2530-83-8) is also known, and will be referred to, as 3-(Trimethoxysilyl)propyl glycidol ether (TMSPGE) or 3-Glycidoxypropyltrimethoxysilane.

Boiling Point

Test Substance

Identity: 3-Glycidoxypropyltrimethoxysilane (CAS No. 2530-83-8)

Remarks Field for Test Substance

Purity of the test substance was measured by gas chromatography and reported as 98%.

Method

Method/guideline followed:	Calculated
GLP (Y/N):	No
Year (study performed):	1985

Remarks Field for Test Conditions

The best-fitting Halm-Stiel vapor pressure equation was used to extrapolate boiling point from vapor pressures measured at temperatures ranging from 100-201°C.

Results

Boiling point value (°C):	262
Pressure:	101.3
Pressure unit:	kPa
Decomposition (yes/no/ambiguous):	no

Remarks Field for Results

- Coefficients for the Halm-Stiel equation were derived from regression of the following measured vapor pressure data:

T (°C)	P (mm Hg)	P (Pa)	Reference
116	4	507	Flaningam 1979
125	5	667	Koetzsch and Vahlensieck 1973
132	10	1280	Flaningam 1979
135	4	533	Plueddemann and Stark 1967
153	23	3066	Flaningam 1979
175	55	7371	Flaningam 1979
200	100	13330	Street 1964
201	140	18595	Flaningam 1979

Conclusions

Remarks Field with Ability to Identify Source of Comment

Although the Halm-Stiel equation is valid for interpolations, serious error may result from extrapolations outside the limits of measured data. Hence, significant error may be associated with the reported boiling point for the test substance (CAS No. 2530-83-8). Nonetheless, the result is comparable to values obtained from the literature and other studies (see Supporting Data).

Data Quality

Remarks Field for Data Reliability

Review of the study report and raw data indicate that the results are scientifically defensible and adequate for assessing the boiling point of the test substance (CAS No. 2530-83-8). The study is considered to be reliable with the following restrictions:

- study was not conducted under GLP
- methods used to generate vapor pressure/temperature data were not documented

References

Key Study: Smith, A.L. 1985. Dow Corning Corporation, Report No. 1985-I0032-0009.

Cited Documents:

- Flaningam, O.L. 1979. Dow Corning Corporation, Report No. 1979-I0039-11.
- Koetzsch, H.J. and H. Vahlensieck. 1973. Silicon containing dioxolane derivatives. German Patent DE2159991.
- Plueddemann, E.P. and G.L. Stark. 1967. Dow Corning Corporation, Report No. 1967-I0030-3216.
- Street, G.L. 1964. Dow Corning Corporation, Report No. 1964-I0030-2312.

Other

Last changed (administrative field for updating):

Order number for sorting (administrative field):

Remarks Field for General Remarks

Supporting Data:

- Reported boiling point of 290°C @ 101.3 kPa. Spivack, J.L., E.R. Pohl, and P. Kochs. 1997. Organoalkoxysilanes, organosilanols, and organosiloxanols, in G. Chandra (ed.), The Handbook of Environmental Chemistry, Vol. 3, Part H, Organosilicon Materials. Springer-Verlag, Berlin, p 105.
- Extrapolated boiling point (Antoine equation) of 263°C @ 101.3 kPa. Flaningam, O.L. 1979. Dow Corning Corporation, Report No. 1979-I0039-11.
- Reported boiling point of 262°C @ 101.3 kPa. Dow Corning Corporation, physical properties database.
- Reported boiling point of 290°C @ 101.3 kPa. General Electric, physical properties database.

Vapor Pressure

Test Substance

Identity: 3-Glycidoxypropyltrimethoxysilane (CAS No. 2530-83-8)

Remarks Field for Test Substance

Purity of the test substance was measured by gas chromatography and reported as 98%.

Method

Method/guideline followed:	Not identified
GLP (Y/N):	No
Year (study performed):	1985

Remarks Field for Test Conditions

The Halm-Stiel and Antoine equations were used to extrapolate vapor pressure at 20°C from vapor pressures measured at elevated temperatures ranging from 100-201°C.

Results

Vapor Pressure value:	0.3 Pa
Temperature (°C):	20
Decomposition (yes/no/ambiguous):	no

Remarks Field for Results

- **Measured vapor pressure and temperature data**

T (°C)	P (mm Hg)	P (Pa)	Reference
116	4	507	Flaningam 1979
125	5	667	Koetzsch and Vahlensieck 1973
132	10	1280	Flaningam1979
135	4	533	Plueddemann and Stark 1967
153	23	3066	Flaningam 1979
175	55	7371	Flaningam 1979
200	100	13330	Street 1964
201	140	18595	Flaningam 1979

The extrapolated vapor pressure of the test substance at 20°C was 0.3 Pa, based on both the Halm-Stiel equation and the Antoine equation.

Conclusions

Remarks Field with Ability to Identify Source of Comment

Although the Halm-Stiel and Antoine equations are valid for interpolations, serious error may result from extrapolations outside the limits of measured data. Hence, significant error may be associated with the estimated vapor pressure of the test substance (CAS No. 2530-83-8) at 20°C. Nonetheless, measured vapor pressures obtained at elevated temperatures are comparable to values obtained from other studies (see Supporting Data).

Data Quality

Remarks Field for Data Reliability

Review of the study report and raw data indicate that the results are scientifically defensible and adequate for assessing the vapor pressure of the test substance (CAS No. 2530-83-8). The study is considered to be reliable with the following restrictions:

- study was not conducted under GLP
- methods used to generate vapor pressure/temperature data were not documented
- vapor pressure at 20°C is extrapolated from vapor pressures measured at elevated temperatures ranging from 100-201°C.

References

Key Study: Smith, A.L. 1985. Dow Corning Corporation, Report No. 1985-I0032-0009.

Cited Documents:

- Flaningam, O.L. 1979. Dow Corning Corporation, Report No. 1979-I0039-11.
- Koetzsch, H.J. and H. Vahlensieck. 1973. Silicon containing dioxolane derivatives. German Patent DE2159991.
- Plueddemann, E.P. and G.L. Stark. 1967. Dow Corning Corporation, Report No. 1967-I0030-3216.
- Street, G.L. 1964. Dow Corning Corporation, Report No. 1964-I0030-2312.

Other

Last changed (administrative field for updating):

Order number for sorting (administrative field):

Remarks Field for General Remarks

Supporting Data: Estimated vapor pressure of 0.3 Pa at 20°C. Dow Corning Corporation, physical properties database.

Biodegradation

Test Substance

- **Identity:** 3-Glycidoxypropyltrimethoxysilane (CAS No. 2530-83-8)

Remarks Field for Test Substance

- **Material tested:** DYNASYLAN GLYMO
- **Purity/components:** 98.0 fluid % CAS No. 2530-83-8

Method

Method/guideline followed:	DOC-DIE AWAY TEST (EWG Guideline 79/831/EWG, Appendix V, Part C (updated edition dated July 1990), Method C.4-A.
Test Type (test type/aerobic/anaerobic):	Aerobic
GLP (Y/N):	Yes
Year (study performed):	1993
Contact time (units):	28 days
Innoculum:	Biological culture from a primarily communal sewage treatment plant (Marl – East)

Remarks Field for Test Conditions

- **Analytical method used to measure biodegradation:** DOC analyses were in the form of a double determination of oxygen-enriched and de-gassed samples (removal of inorganic carbon), membrane filter with pore size of 0.2 µm. The DOC analysis was performed using two-point calibration in a carbon analyzer (Shimadzu).

Results

Degradation % after time: Duplicates run with test article. Flask 1: Percent degradation after 0, 7, 14, 21, 27 and 28 days was 0, 31, 34, 31, 43 and 37%, respectively. Flask 2: Percent degradation after 0, 7, 14, 21, 27 and 28 days was 0, 31, 34, 35, 40, and 37%, respectively.

Results: Mean percent degradation for test article: 0, 31, 34, 33, 41, and 37% for 0, 7, 14, 21, 27, and 28 days, respectively.

Kinetic (for sample, positive and negative controls): For each time period %, sample % degradation for each time period noted above. For positive control, sodium benzoate, > 96% degradation was reported for each time period in both duplicate samples, and was 100% DOC reduction within 28 days. For the negative control, % degradation was not calculated, but raw data indicates no degradation at any of the time periods measured.

Breakdown products (yes/no): DYNASYLAN GLYMO is known to be hydrolytically unstable. When added to water, it rapidly hydrolyzes, generating methanol and silanetriol derivatives. Therefore, results from this study likely represent biodegradation of methanol rather than the parent material.

Conclusions

Remarks Field with the Ability to Identify Source of Comment

Author: DYNASYLAN GLYMO achieved a breakdown rate of 37%(DOC reduction) within 28 days. Based on these findings, DYNASYLAN GLYMO was determined as "not readily biodegradable". The control substance, sodium benzoate, achieved a breakdown rate of 99.5% (DOC reduction) within 10 days and 100% within 28 days. This leads to the conclusion that the culture used possessed adequate biological activity.

Data Quality

Remarks Field for Data Reliability

References

Hüls AG, Testing Institute for Biology. Final Report DDA 53. Determination of the biodegradability of DYNASYLAN GLYMO in DOC-DIE AWAY TEST. February 2, 1994.

Other

Last changed (administrative field for updating):

Order number for sorting (administrative field):

Acute Toxicity to Fish

Test Substance

Identity: 3-Glycidoxypropyltrimethoxysilane (CAS No. 2530-83-8)

Remarks Field for Test Substance

Purity of the test substance was measured by gas chromatography and reported as 98%. The test substance is not stable in water and rapidly hydrolyzes to methanol and 3-glycidoxypropyl-silanetriol (R-$Si(OH)_3$ where R = $-(CH_2)_3OCH_2CHOCH_2$). The hydrolysis half-life for the test substance is estimated to be 4 hours at pH 7 (Pohl and Osterholtz 1985).

Method

Method/guideline followed:	EPA-660/3-75-009 (USEPA 1975).
Type (test type):	Static acute toxicity (lethality); freshwater fish.
GLP (Y/N):	No
Year (study performed):	1978
Species/Strain/Supplier:	Rainbow trout (*Oncorhynchus mykiss,* identified as *Salmo gairdnerii*) obtained from Fenders Fish Hatchery, Baltic, Ohio (USA).
Analytical monitoring:	None
Element basis:	mortality (lack of movement when prodded)
Exposure period:	96 hours
Statistical methods:	Probit analysis (Finney 1952)

Remarks Field for Test Conditions

- **Design:** static exposure, no solution renewal
- **Dilution water:** reconstituted soft-water prepared from glass-distilled water, EPA-660/3-75-009 (USEPA 1975)
- **Water chemistry:** not documented (except for pH and dissolved oxygen)
- **Test substance stability:** test substance not stable in aqueous solutions; estimated hydrolysis half-life of 4 hours at pH 7
- **Exposure vessel:** polyethylene-lined vessels containing 10 L of dilution water; vessels aerated prior to study initiation but not during study
- **Dosing solutions:** no dosing solutions used; test material added directly to exposure vessels
- **Carrier solvent:** none
- **Exposure concentrations:** nominal - 0, 10, 32, 100, 135, 180, 240, 320, 1000 mg/L; measured - concentrations not analytically verified
- **Replication:** duplicate controls; single exposure concentrations

- **Test system:** juvenile rainbow trout having a mean total length of 7.1 cm (range 5.5-8.4 cm); fish were acclimated to laboratory conditions a minimum of two weeks before testing; loading rate of 10 fish per exposure vessel (9 fish in 135, 180, and 240 mg/L exposure concentrations); total of 97 fish
- **Observation periods:** 0, 24, 48, 72, 96 h after study initiation
- **Photo-period:** not specified
- **Temperature:** 12°C in water bath (mean and ranges not reported)
- **Dissolved oxygen:** initiation (t = 0 h): mean 12.5 mg/L (range 11.5-13.0 mg/L); termination (t = 96 h): mean 5.1 mg/L (range 3.5-7.0 mg/L)
- **pH:** initiation (t = 0 h): mean 7.3 (range 7.2-7.4); termination (t = 96 h): mean 7.3 (range 7.3-7.4)

Results

(mg/L nominal concentrations)

- 96-h NOEC = 180
- 96-h LOEC = 240
- 96-h LC_{100} = 320
- 96-h LC_{10} = 198 (139-220; 95% CI)
- 96-h LC_{50} = 237 (208-268; 95% CI)
- 96-h LC_{90} = 283 (255-398; 95% CI)

Remarks Field for Results

No mortality observed in controls. Sublethal effects (stressed, loss of equilibrium, air gulping) observed in 240 mg/L exposure (LOEC) at 72-h observation. Sublethal effects (dark pigmentation, quiescence) observed in 320 mg/L exposure (LC_{100}) at 24-h observation.

	Cumulative Mortality (%)				
Concentration (mg/L)	0 Hours	24 Hours	48 Hours	72 Hours	96 Hours
0	0	0	0	0	0
10	0	0	0	0	0
32	0	0	0	0	0
100	0	0	0	0	0
135	0	0	0	0	0
180	0	0	0	0	0
240	0	0	0	10	60
320	0	0	10	100	100
1000	0	100	100	100	100

Conclusions

Remarks Field with Ability to Identify Source of Comment

Based on results from the study (NOEC = 180 mg/L, LOEC = 240 mg/L, and LC_{50} = 237 mg/L), the test substance and hydrolytic degradation products are considered practically non-toxic (LC_{50} > 100 mg/L) to rainbow trout under the described conditions of exposure. The NOEC and LOEC obtained from this study are greater than those for bluegill sunfish (see Supporting Data). However, the LC_{50} is slightly less than that obtained for bluegill sunfish.

Data Quality

Remarks Field for Data Reliability

Study is considered to be reliable with the following restrictions:

- study was not conducted under GLP
- exposure concentrations were not analytical verified
- exposure concentrations were not replicated
- temperature not documented for entire study

References

Key Study: Annelin, R.B. and J.E. Cerro. 1978. Dow Corning Corporation, Report No. 1978-I0005-0581.

Cited Documents:

- Finney, D.J. 1952. *Statistical Method in Biological Assay.* New York, Hafner, 661 p.
- Pohl, E.R. and F.D. Osterholtz. 1985. Kinetics and mechanism of aqueous hydrolysis and condensation of alkyltrialkoxysilanes. *Polym. Sci. Technol.* 27:157-170.
- USEPA. 1975. Methods for acute toxicity tests with fish, macroinvertebrates, and amphibians. United States Environmental Protection Agency, EPA-660/3-75-009.

Other

Last changed (administrative field for updating):

Order number for sorting (administrative field):

Remarks Field for General Remarks

Supporting Data: Annelin, R.B. and J.E. Cerro. 1978. Dow Corning Corporation, Report No. 1978-I0005-0581. The static acute toxicity of the test substance (CAS No. 2530-83-8; purity reported as 98%) to bluegill sunfish (*Lepomis macrochirus*) was determined in reconstituted soft water following guideline EPA-660/3-75-009 (USEPA 1975). Juvenile bluegill sunfish (size not documented) were exposed in single replicates (loading rate of 10 fish per vessel) to nominal concentrations of 0, 10, 32, 100, 320, and 1000 mg/L. The test substance was added directly to the exposure vessels (polyethylene-lined containers with 10 L of dilution water), a carrier solvent was not used. The non-GLP study was conducted at 22°C. Exposure concentrations were not analytically verified. Mean dissolved oxygen was 13.3 mg/L (range 13.0-13.5 mg/L) at test initiation and 8.5 mg/L (range 8.0-9.0 mg/L) at test termination. Mean pH was 7.2 (range 7.2-7.3) at test initiation and was not recorded at test termination. Results from the study were reported as follows (mg/L, nominal concentrations):

- 96-h NOEC = 32
- 96-h LC_{10} = 59 (13-114; 95% CI)

- 96-h LOEC = 100
- 100% mortality = 1000
- 96-h LC_{50} = 276 (152-572; 95% CI)
- 96-h LC_{90} > 1000 (610-8396; 95% CI)

Based on results from the study (NOEC = 32 mg/L, LOEC = 100 mg/L, and LC_{50} = 276 mg/L), the test substance and hydrolytic degradation products are considered practically non-toxic (LC_{50} > 100 mg/L) to bluegill sunfish under the described conditions of exposure. The NOEC, LOEC, and LC_{50} obtained from this study are nearly identical to those for rainbow trout (see Key Study).

The NOEC and LOEC obtained from this study are less than those for rainbow trout (see Key Study). However, the LC_{50} is slightly greater than that obtained for rainbow trout.

This study was not conducted in full compliance with OECD 203. However, the study design, documentation of data, and results are considered scientifically defensible and adequate for assessing the acute toxicity of the test substance (CAS No. 2530-83-8) to freshwater fish. The study is considered to be reliable with the following restrictions:

- study was not conducted under GLP
- exposure concentrations were not analytical verified
- exposure concentrations were not replicated
- temperature not documented for the entire study
- fish size was not documented
- sublethal effects were not documented

Toxicity to Aquatic Plants (e.g., Algae)

Test Substance

Identity: 3-Glycidoxypropyltrimethoxysilane (CAS No. 2530-83-8).

Remarks Field for Test Substance

Purity of the test substance was measured by gas chromatography and reported as 98%. The test substance is not stable in water and rapidly hydrolyzes to methanol and 3-glycidoxypropyl-silanetriol ($R\text{-}Si(OH)_3$ where $R = -(CH_2)_3OCH_2CHOCH_2$). The hydrolysis half-life for the test substance is estimated to be 4 hours at pH 7 (Pohl and Osterholtz 1985).

Method

Method/guideline followed:	EPA-670/4-73-00 (USEPA 1973)
Type (test type):	Static acute toxicity (growth inhibition and final yield) to freshwater blue-green algae
GLP (Y/N):	No
Year (study performed):	1978
Species/Strain/Supplier:	Blue-green algae (*Anabaena flos-aquae*); laboratory culture (source of original culture not documented)
Element basis:	cells/mL (direct counts, in duplicate, using a hemocytometer) and growth rate
Exposure period, date of start and end of the test:	7 days, 23-30 August 1978
Analytical monitoring:	No
Statistical methods:	Probit analysis (Finney 1952); calculations as described by Stein (1973)

Remarks Field for Test Conditions

- **Test design:** static exposure, no solution renewal
- **Growth medium:** sterile algal broth prepared from glass-distilled water and powdered nutrient media (Difco® Laboratories); source of dilution water not documented
- **Water chemistry:** not documented
- **Test substance stability:** test substance not stable in aqueous solutions; estimated hydrolysis half-life of 4 hours at pH 7
- **Exposure vessel:** 125-mL polycarbonate Erlenmeyer flasks containing 40 mL of sterile algal broth; aseptic technique used throughout study
- **Dosing solutions:** no dosing solutions used; neat test material added directly to exposure vessels
- **Carrier solvent:** none

- **Exposure concentrations:** nominal - 0, 50, 100, 1000, 10,000 mg/L; measured - concentrations not analytically verified
- **Replication:** triplicate controls and exposure concentrations
- **Test system:** *Anabaena flos-aquae*, 1.00×10^4 cells/mL at test initiation, laboratory culture (original source and method of cultivation not documented)
- **Observation periods:** 0, 3, 4, 5, 6, 7 d after study initiation
- **Photo-period:** 18-h light/6-h dark; 600 foot-candle
- **Temperature:** 23 ± 1°C in environmental chamber
- **pH:** not documented

Results

Final Yield (mg/L nominal concentrations)

- 7-d NOEC = 0
- 7-d LOEC = 50
- 7-d EC_{10} = 26 (11-46; 95% CI)
- 7-d EC_{50} = 268 (185-370; 95% CI)
- 7-d EC_{90} = 2742 (1777-5003; 95% CI)

Growth Inhibition (mg/L nominal concentrations)

- 7-d NOEC = 0
- 7-d LOEC = 50
- 7-d EC_{10} = 40 (29-49; 95% CI)
- 7-d EC_{50} = 119 (101-147; 95% CI)
- 7-d EC_{90} = 357 (259-595; 95% CI)

Remarks Field for Results

Response of the controls was acceptable with exponential growth demonstrated (cell concentration in the controls increased by a factor of 13.5 over the 7-day study).

	Final Yield ($\times 10^4$ cells/mL)					
Concentration (mg/L)	0 Days	3 Days	4 Days	5 Days	6 Days	7 Days
0	1.00	3.87	5.55	9.17	9.90	13.5
50	1.00	3.65	4.78	6.36	9.60	10.2
100	1.00	4.05	4.91	7.10	8.51	10.3
1000	1.00	1.26	1.28	1.21	1.45	1.82
10,000	1.00	0.74	0.74	0.72	0.81	0.77

	Growth Inhibition (%)					
Concentration (mg/L)	0 Days	3 Days	4 Days	5 Days	6 Days	7 Days
0	0	0	0	0	0	0
50	0	6	14	31	3	24
100	0	-5	12	23	14	24
1000	0	67	77	87	85	87
10,000	0	81	87	92	92	94

Conclusions

Remarks Field with Ability to Identify Source of Comment

Based on results from the study for final yield (NOEC = 0 mg/L, LOEC = 50 mg/L, and EC_{50} = 268 mg/L) and growth inhibition (NOEC = 0 mg/L, LOEC = 50 mg/L, and EC_{50} = 119 mg/L), the test substance and hydrolytic degradation products are considered practically non-toxic (LC_{50} > 100 mg/L) to *Anabaena flos-aquae* (blue-green algae) under the described conditions of exposure.

Data Quality

Remarks Field for Data Reliability

Study is considered to be reliable with the following restrictions:

- study was not conducted under GLP
- original supplier of the test system not documented
- cultivation methods for laboratory culture not documented
- source of dilution water not documented
- water chemistry not documented
- exposure concentrations not analytical verified

References

Key Study: Annelin, R.B. and J.E. Cerro. 1978. Dow Corning Corporation, Report No. 1978-I0005-0581.

Cited Documents:

- Finney, D.J. 1952. *Statistical Method in Biological Assay.* New York, Hafner, 661 p.
- Pohl, E.R. and F.D. Osterholtz. 1985. Kinetics and mechanism of aqueous hydrolysis and condensation of alkyltrialkoxysilanes. *Polym. Sci. Technol.* 27:157-170.

Other

Last changed (administrative field for updating):

Order number for sorting (administrative field):

Acute Toxicity to Aquatic Invertebrates (e.g., Daphnia)

Test Substance

Identity: 3-Glycidoxypropyltrimethoxysilane (CAS No. 2530-83-8)

Remarks Field for Test Substance

Purity of the test substance was measured by gas chromatography and reported as 98%. The test substance is not stable in water and rapidly hydrolyzes to methanol and 3-glycidoxypropyl-silanetriol (R-$Si(OH)_3$ where R = $-(CH_2)_3OCH_2CHOCH_2$). The hydrolysis half-life for the test substance is estimated to be 4 hours at pH 7 (Pohl and Osterholtz 1985).

Method

Method/guideline followed:	EPA-660/3-75-009 (USEPA 1975)
Type (test type):	Static acute toxicity (immobility) to freshwater macroinvertebrate
GLP (Y/N):	No
Year (study performed):	1978
Species/Strain/Supplier:	*Simocephalus vetulus* (Family Daphnidae) obtained from Ward's Scientific (culture mistakenly identified as *Daphnia magna*).
Analytical procedures:	Concentrations of test material not analytically verified.
Test details:	static, 48-h exposure with the effect endpoint identified as immobilization (no movement after gentle agitation of test chamber)
Statistical methods:	Probit analysis (Finney 1952)

Remarks Field for Test Conditions

- **Test design:** static exposure, no solution renewal
- **Dilution water:** reconstituted hard-water; glass-distilled water reconstituted with 192 mg/L $NaHCO_3$, 120 mg/L $CaSO_4$, 120 mg/L $MgSO_4$, and 8 mg/L KCl (pH adjusted to 7.5 with NaOH)
- **Water chemistry:** not documented
- **Test substance stability:** test substance not stable in aqueous solutions; estimated hydrolysis half-life of 4 hours at pH 7
- **Exposure vessel:** 250-mL glass beakers containing 200 mL of dilution water; vessels aerated prior to but not after study initiation; vessels covered with Saran Wrap® during exposure
- **Dosing solutions:** no dosing solutions used; neat test material added directly to exposure vessels
- **Carrier solvent:** none
- **Exposure concentrations:** nominal - 0, 100, 250, 300, 350, 400, 450, 500 mg/L; measured - concentrations not analytically verified.

- **Replication:** duplicate controls and exposure concentrations
- **Test system:** *Simocephalus vetulus* neonates (age not documented) from laboratory cultures maintained under testing conditions; loading rate of 10 organisms per exposure vessel; total of 160 organisms
- **Observation periods:** 0, 24, 48 h after study initiation
- **Photo-period:** 18-h light/6-h dark; 600 foot-candle
- **Temperature:** 23 ± 1°C in environmental chamber
- **Dissolved oxygen:** not documented
- **pH:** mean 7.5 (range 7.4-7.7)

Results

(mg/L nominal concentrations)

- 96-h NOEC = 100
- 96-h LOEC = 250
- 96-h EC_{100} = 500
- 96-h EC_{10} = 248 (212-272; 95% CI)
- 96-h EC_{50} = 324 (301-343; 95% CI)
- 96-h EC_{90} = 422 (393-474; 95% CI)

Remarks Field for Results

No immobilization observed in controls. One immobilization (5%) observed in 100 mg/L exposure (NOEC) at 24-h observation—was not considered dose related. Sublethal effects, if any, were not recorded.

	Cumulative Mortality (%)		
Concentration (mg/L)	0 Hours	24 Hours	48 Hours
0	0	0	0
100	0	5	5
250	0	5	20
300	0	5	25
350	0	20	55
400	0	15	90
450	0	15	95
500	0	30	100

Conclusions

Remarks Field with the Ability to Identify Source of Comment

The test substance is considered practically non-toxic (LC_{50} > 100 mg/L) to *Simocephalus vetulus* (Family Daphnidae) under the described conditions of exposure.

Based on results from the study (NOEC = 100 mg/L, LOEC = 250 mg/L, and EC_{50} = 324 mg/L) the test substance and hydrolytic degradation products are considered practically non-toxic (LC_{50} > 100 mg/L) to *Simocephalus vetulus* (Family Daphnidae) under the described conditions of exposure.

Data Quality

Remarks Field for Data Reliability

Study is considered to be reliable with the following restrictions:

- study was not conducted under GLP
- exposure concentrations were not analytical verified
- age of neonates not documented
- sublethal effects not documented
- dissolved oxygen not documented

References

Key Study: Annelin, R.B. and J.E. Cerro. 1978. Dow Corning Corporation, Report No. 1978-I0005-0581.

Cited Documents:

- Finney, D.J. 1952. *Statistical Method in Biological Assay.* New York, Hafner, 661 p.
- Pohl, E.R. and F.D. Osterholtz. 1985. Kinetics and mechanism of aqueous hydrolysis and condensation of alkyltrialkoxysilanes. *Polym. Sci. Technol.* 27:157-170.
- USEPA. 1975. Methods for acute toxicity tests with fish, macroinvertebrates, and amphibians. United States Environmental Protection Agency, EPA-660/3-75-009.

Other

Last changed (administrative field for updating):

Order number for sorting (administrative field):

Acute Oral Toxicity

Test Substance

Identity: 3-Glycidoxypropyltrimethoxysilane (CAS No. 2530-83-8)

Method

Method/guideline followed:	The design of the study generally conforms to that described in OECD Health Effects Test Guideline No. 401 (February 24, 1987).
Type/Test Type:	Acute oral toxicity in rats
GLP (Y/N):	No
Year (study performed):	1976
Species/Strain:	Rat/Wistar
Sex:	Male and female
No. of animals per sex per dose group:	Range-finding study: 1 LD_{50} study: 5
Vehicle:	Range-finding study: Cottonseed oil, except dosed undiluted at high dose LD_{50} study: Not applicable; test substance dose undiluted
Route of administration:	Oral via gastric intubation (gavage)

Remarks Field for Test Conditions

Each rat received a single dose of the test substance. The rats weighed 200 $\pm$ 2 grams at dosing and were fasted overnight prior to test substance administration. Rats on the range-finding study received 2.5, 5.0 or 12.5 mL/kg of a 20% test substance mixture in cottonseed oil or 5.0 mL/kg of undiluted test substance, equivalent to dose levels of 0.47, 0.93, 2.34 and 4.76 g/kg. Rats on the LD50 study received 3.9, 5.0, 6.3, 10.0 or 12.6 mL/kg of undiluted test substance, equivalent to 3.6, 4.7, 5.9, 9.3 and 11.8 g/kg. Rats on the range-finding study were observed for seven days. Rats on the LD_{50} study were observed immediately after dosing and daily thereafter for fourteen days. Gross necropsies were not performed.

Results

Value [LD_{50} or LC_{50}] with confidence limits: The acute median lethal dose (LD_{50}) with 95% confidence limits, calculated by the method of Litchfield and Wilcoxon, J. *Pharm. Exp. Thera.*, 96, 99 (1949) was 7.01 (5.61-8.76) g/kg.

Number of deaths at each dose level: No deaths occurred on the dose range-finding study. On the LD_{50} study, within one hour of dosing, clinical signs of piloerection and lethargy were observed, followed by coma and death in some animals. All deaths occurred within 48 hours of dosing and all survivors were asymptomatic after that time. Mortality rates were 1/10, 3/10, 3/10, 7/10 and 8/10 for the 3.6, 4.7, 5.9, 9.3 and 11.8 g/kg groups, respectively.

Conclusions

Results Field with Ability to Identify Source of Comment

Although this study was not conducted in full conformance with OECD test guidelines, it is more than adequate to assess the acute oral toxicity study of the test substance. The test substance has a very low order of toxicity in rats by the oral route of exposure. The LD_{50} study was preceded by a dose range-finding study. There was an excellent dose response on the LD_{50} study, and the calculated LD_{50} exceeds the current the OECD and EPA limit test level more than three-fold.

Data Quality

Remarks Field for Data Reliability

Based a review of the report, the study was judged to be scientifically defensible.

References

Key Study: Dow Corning Corporation internal report number 1976-I0065-1167-30.

Other

Last changed (administrative field for updating):

Order number for sorting (administrative field):

Remarks Field for General Remarks

Supporting Data:

- *Acute Oral Toxicity in Rats (Allied Corporation Project No. MA-31-78-1).* In an acute oral toxicity study in rats conducted in 1978, six groups of ten to twelve rats received oral doses of the test substance of 14.0, 14.4, 15.5, 16.3, 17.1, or 18.0 g/kg. The rats were observed for 14 days and those that died were necropsied. Mortalities were 0%, 0%, 9%, 40%, 58% and 80%, respectively, at the above dosages. The LD_{50} was 16.9 g/kg with 95% confidence limits of 16.4-17.4 g/kg. Remarkable clinical signs seen at the higher dosages were reductions in spontaneous activity, reactivity and respiration and loss of motor coordination. Dark areas on the liver margins and some hemorrhaging in the lungs were seen in some rats that died. The test substance has a very low order of toxicity in rats by the oral route of exposure.

Acute Inhalation Toxicity

Test Substance

Identity: 3-Glycidoxypropyltrimethoxysilane (CAS No. 2530-83-8)

Method

Method/Guideline Followed:	OECD Health Effects Test Guideline No. 403 (May 12, 1981)
Type/Test Type:	Acute inhalation toxicity in rats
GLP (Y/N):	Yes
Year (study performed):	1981
Species/Strain:	Rat/Fischer 344
Sex:	Male and female
No. of animals per sex per dose group:	5
Vehicle:	Not applicable; atmospheres generated using undiluted test substance
Route of Administration:	Whole body inhalation exposure (dynamic)

Remarks Field for Test Conditions

Each rat received a single exposure to the aerosolized test substance. The duration of the exposures was four hours plus the period of time required for the aerosol to clear from the chambers prior to animal removal. The rats were approximately 11 weeks of age and weighed 242 $\pm$ 9 grams (males) and 149 $\pm$ 5 grams (females) at exposure. Exposure concentrations were 0 (air control), 0.8, 1.9 and 5.3 mg/L.

Exposure concentrations were measured using gravimetric methods. Analysis of concomitant test atmosphere samples by gas chromatography was also performed. The gas chromatographic data were considered secondary due to recovery inefficiencies, however, gas chromatographic values averaged 85% of the gravimetrically determined concentrations. Mass median aerodynamic diameter was determined hourly by cascade impaction for each exposure level and ranged from 1.4 to 2.0 microns. Average chamber temperature and relative humidity ranges were 71-73 °F and 69-78%, respectively.

The rats were observed during the four hour period immediately following completion of exposure and daily thereafter for 14 days. All rats were weighed 1, 2, 4 or 5, 7 and 14 days after exposure. Surviving animals were euthanized on day 14. Gross necropsies were performed on all rats.

Results

A median lethal concentration (LC_{50}) could not be calculated because less than 50% of the animals died at the highest exposure level, however, the four-hour inhalation LC_{50} in rats can be estimated to be greater than 5.3 mg/L.

No deaths occurred at the two lower concentrations (1.9 and 0.8 mg/L). At the highest concentration (5.3 mg/L), three rats died, one male on day 1, one female on day 1 and one female on day 2. Following exposures, all rats exhibited varying amounts of test substance contamination on the fur. Clinical signs included excessive lacrimation, dry and moist rales, nasal discharge, and yellow staining in the anal-genital area. These signs were considered to be dose-related and were not generally observed during the second week following exposure. There was also a transient dose-related body weight depression seen in all groups (including the control) during the first week, however, mean body weights exceeded pre-exposure values by day 14 in all groups. Discolored lungs and autolytic changes were seen in the three rats that died. There were no gross abnormalities noted at the necropsy of survivors.

Conclusions

Remarks Field with Ability to Identify Source of Comment

The test substance has a very low order of toxicity in rats by inhalation. The estimated LC_{50} exceeds current OECD and EPA limit test exposure levels.

Data Quality

Remarks Field for Data Reliability

Based on a review of the report, the study was judged to be scientifically defensible.

References

Key Study: Allied Corporation Report No. MA-168-81-6; Dow Corning Corporation internal report number 1982-I0065-1167-18.

Other

Last changed (administrative field for updating):

Order number for sorting (administrative field):

Genetic Toxicity *In Vitro* (Gene Mutations)

Test Substance

Identity: 3-Glycidoxypropyltrimethoxysilane (CAS No. 2530-83-8)

Method

Method/Guideline Followed:	The study was conducted in general conformance with OECD Health Effects Test Guideline No. 471 (May 26, 1983).
Type/Test Type:	Reverse mutation assay
System of Testing:	Bacterial and non-bacterial
GLP (Y/N):	No
Year (study performed):	1977
Species:	*Salmonella typhimurium* and *saccharomyces cervisiae*
Strains:	*S. typhimurium*: TA-98, TA-100, TA-1535, TA-1537 and TA-1538
Metabolic Activation:	Yes, both with and without • **Species and cell type:** Rat liver • **Quantity:** 0.1 to 0.15 ml of a 9000 x g supernatant of rat liver homogenate per ml of reaction mixture • **Induced or Not Induced:** Yes; Arochlor 1254
Concentrations Tested:	0.001, 0.001, 0.1, 1.0, 5.0, 10.0 and 20.0 µl/plate (Plate Incorporation Method)
Statistical Methods:	Responses (numbers of revertants) to the test substance were compared to concurrent negative and positive controls, as well as to historical data.

Remarks Field for Test Conditions

The control and test substances were administered once. The solvent (negative control) for all treatments/strains was dimethylsulfoxide (DMSO), 50 µl/plate.

Positive Control Agents and Doses (µg/plate)

	TA-98	TA-100	TA-1535	TA-1537	TA-1538	D4
Activation	AAF(100)	ANT(100)	ANT(100)	AMQ(100)	AAF(100)	DMNA*
Non-activation	NF(100)	MNG(10)	MNG(10)	QM(10)	NF(100)	MNG(10)

AAF = 2-Acetylaminofluorene
ANT = 2-Anthracine
AMQ = 8-Aminiquinolone
MNG = Methylnitrosoguanidine
DMNA = Dimethylnitrosamine
NF = Nitrofluorene
QA = Quinicrine mustard
* = 100 µmol/plate

The plates were incubated for 72 hours at 37°C, and then counted. The number of cells evaluated per dose group was not reported. Revertants per plate for positive control substances ranged from 200 to >1000, depending on the agent and strain.

Results

The test substance was clearly mutagenic in the TA-100 and TA-1535 strains, both with and without metabolic activation. Dose-related increases in the numbers of revertants were seen for TA-100 at treatment concentrations of 1 and 5 µl/plate (the highest levels tested for this strain). Dose-related increases in the numbers of revertants were seen for the TA-1535 strain at treatments concentrations of 5.0, 10.0 and 20.0 µl/plate. In addition, the numbers of TA-1535 revertants at treatments of 0.1 and 1.0 µl/plate (activation assay) were approximately two times the solvent control. No evidence of mutagenic activity was present for any of the other strains that were tested.

Conclusions

Remarks Field with Ability to Identify Source of Comment

Appropriate concurrent negative and positive controls were included, and the expected responses were observed. The test substance, 3-glycidoxypropyltrimethoxysilane (CAS No. 2530-83-8), induced mutagenicity in the TA-100 and TA-1535 strains, both with and without metabolic activation. No mutagenic activity was seen in any of the other strains that were tested. The results indicate that the test substance induces missense mutations and does not require metabolic activation to be genetically active.

Data Quality

Remarks Field for Data Reliability

Based on a review of the report, the study was judged to be scientifically defensible.

References

Key Study: Litton Bionetics, Inc. Project No. 2838; Dow Corning Corporation internal report no. 1977-I0065-1167-04.

Other

Last changed (administrative field for updating):

Order number for sorting (administrative field):

Supporting Data:

- *Mutagenicity Evaluation of [3-Glycidoxypropyltrimethoxysilane] in the Mouse Lymphoma Assay and a Microbial Suspension Assay (Litton Bionetics, Inc. Project No. 2684).* In a study conducted in 1976, the mutagenic potential of the test substance was assessed in Fischer mouse lymphoma cells (forward mutation) and in the TA-1535 strain of *Salmonella Typhimurium* (reverse mutation), both under non-activation conditions. Negative controls (tissue culture medium or DMSO, as appropriate) and a positive control (ethylmethanesulfonate, 200 µg/ml) were included. Mouse lymphoma cells were exposed to test substance concentrations of 0.33, 0.65, 1.30, 2.60 and 5.20 µl/ml. Mutation frequency ratios were increased at the 0.65, 1.30 and 2.60 concentrations in a dose-response; the test substance was cytotoxic at 5.20 µl/ml. The TA-1535 bacteria were exposed to concentrations of 1, 5, 10, 50, 100, 500 and 1000 µl/ml. The test substance was mutagenic at the 50, 100 and 500 µl/ml concentrations, as evidenced by dose-related fold-increases in the numbers of revertants, and possibly at 10 µl/ml, where the number of revertants was nearly two times the solvent control. Cytotoxicity was observed at 1000 µl/ml.
- *Mutagenicity Evaluation of [3-Glycidoxypropyltrimethoxysilane] in the Ames Bacterial Assay System (Dow Corning Corporation internal report number 1977-I0005-524).* In a study conducted in 1977, the test substance was evaluated for genetic toxicity in the *Salmonella typhimurium* reverse mutation assay. Bacteria (TA-1535, TA-1537, TA-1538, TA-98, and TA-100 strains) were exposed to the test substance in the presence or absence of a mammalian activation system (Aroclor 1254-induced rat liver [S-9]). Four concentrations of the test substance (5, 50, 200, and 500 µg/plate) were tested. Dimethylsulfoxide was used to prepare the dilutions of the test substance and as a negative (solvent) control. Appropriate positive controls were included. A dose-related increase in mutation frequency was seen for the TA-100 and TA-1535 strains at all treatment concentrations, both with and without activation. No evidence of genetic activity was seen in the other strains that were tested. It was concluded that the test substance induced base-pair substitutions and did not require metabolic activation to be genetically active.
- *Evaluation of [3-Glycidoxypropyltrimethoxysilane] for Enzyme Mediated Mutagenicity in Salmonella Typhimurium (Allied Corporation Project No. MA-52):* In a study conducted in 1978, the mutagenic potential of the test substance was evaluated in a reverse mutation assay using five strains of *S typhimurium,* TA-98, TA-100, TA-1535, TA-1537 and TA-1538. Concentrations of 5, 50, 500 and 5000 µg/plate were tested, both with and without a mammalian activation system (Aroclor 1254-induced rat liver [S-9]). Dimethylsulfoxide was used to prepare the dilutions of the test material and as a negative (solvent) control. Appropriate positive controls were included. The authors of this report incorrectly concluded that the test substance did not increase the number of revertants in any strains tested. Clear, dose-responsive, multi-fold increases in the numbers of revertants were present for the TA-100 and TA-1535 strains at concentrations of 500 and 5000

µg/plate, both with and without metabolic activation. No increase in mutation frequency was observed for the other strains or concentrations that were tested.

- *Mutagenicity Evaluation of [3-Glycidoxypropyltrimethoxysilane] in the Ames Bacterial Assay (Dow Corning Corporation internal report number 1979-I0005-676).* The test substance was one of four materials included in this 1979 evaluation of mutagenic potential using the *Salmonella typhimurium* reverse mutation assay. Bacteria (TA-1535, TA-1537, TA-1538, TA-98, and TA-100 strains) were exposed to the test substance in the presence or absence of a mammalian activation system (Aroclor 1254-induced rat liver [S9]). Four concentrations of the test substance (5, 50, 100, and 500 µg/plate) were tested. Dimethylsulfoxide was used to prepare the dilutions of the test material and as a negative (solvent) control (50 µl/plate). Appropriate positive controls were included. There was an increase in mutation frequency in strains TA-1535 and TA-100 at 500 µg/plate both with and without metabolic activation, for the TA-1535 strain at 100 µg/plate (activation assay) and for the TA-100 strain at 100 µg/plate (non-activation assay). It was concluded that the test substance induced bacterial mutations and did not require metabolic activation to be genetically active.
- *Evaluation of [3-Glycidoxypropyltrimethoxysilane] for Mutagenicity in Salmonella Typhimurium (Allied Corporation Report No. MA-168-81-5; Dow Corning Corporation internal report number 1982-I0065-1167-17).* In a confirmatory study conducted in 1982, the mutagenicity of the test substance was examined in the *Salmonella typhimurium* reverse mutation assay. A single bacterial strain, TA-100, was exposed to the test substance without metabolic activation. Four concentrations (0.05, 0.1, 0.5, and 1.0 µg /plate) were tested. Dimethylsulfoxide was used to prepare the dilutions of the test material and as a negative (solvent) control (50 µl/plate). Sodium azide (1.0 µg/plate) was employed as the positive control. This sample induced a dose-related response at all doses tested. Under the conditions of this study, the test material was found to be mutagenic, and that metabolic activation was not required.
- *Evaluation of [3-Glycidoxypropyltrimethoxysilane] for Mammalian Cell Mutagenicity in Chinese Hamster Ovary (CHO) Cells (Allied Corporation, Project no. MA-52A).* In a study conducted in 1979, the ability of the test substance to induce forward mutations in Chinese hamster ovary cells was assessed. Cultures CHO cells were exposed to the test substance at concentrations of 10 through 1000 µg/ml, both with and without rat liver S-9 activation. Dimethylsulfoxide was used to prepare the dilutions of the test material and as a negative (solvent) control (50 µl/plate). Positive controls (methylmethane sulfonate and dimethylnitrosamine) were included. There was no increase in mutation rate observed at any dose tested.
- *Evaluation of [3-Glycidoxypropyltrimethoxysilane] in the Sister Chromatid Exchange (SCE) Test: In Vitro results in Chinese Hamster Ovary Cells (Allied Corporation Report No. MA-168-81-7; Dow Corning Corporation internal report number 1982-I0065-4122-04).* In a study conducted in 1982, the test substance was evaluated for its ability to induce sister chromatid exchanges (SCE) in Chinese hamster ovary (CHO) cells. The test substance was diluted in dimethylsulfoxide, which was also used as the negative control (0.1 ml/flask). A positive control group (mitomycin-C, 3×10^{-8} M) was included. CHO cells were exposed to the test substance (0.02, 0.04, 0.06, 0.08, and 0.1 mg/ml). At the end of a two hour incubation period, the medium was discarded and cells were washed with sterile saline. Fresh medium was added together with bromodeoxyuridine (BrdU; 10 µl). After approximately 27 hours, the mitotic cells were harvested, fixed, and dropped onto microslides for staining and SCE analysis. The test material produced increases in SCE in a dose-related manner in CHO cells at the 0.04, 0.06, 0.08 and 0.10 concentrations. Although the actual numbers of SCE were low (less than a two-fold increase over untreated controls), the concentrations of the test

material were also low (higher concentrations were cytotoxic) and the increases were statistically significant (as well as dose-responsive). Therefore, it was concluded that the test article was a moderate *in vitro* inducer of SCE.

- *In Vitro Mammalian Cell Transformation Assay of [3-Glycidoxypropyltrimethoxysilane] (Dow Corning Corporation internal report number 1981-I0005-830).* In a GLP study conducted in 1980, the test substance was evaluated for its ability to induce malignant transformation of BALB/3T cells *in vitro.* Exponentially-growing BALB/3T cells were incubated for 72 hours with the test material at concentrations of 8.3, 12.5, and 16.6 μg/ml. The test substance was diluted in dimethylsulfoxide, which was also used as the negative control (2.5×10^3 μg/ml). A positive control group (N-methyl-N'-nitro-N-nitrosoguanidine, 0.5 μg/ml) was included. After incubation, the medium was discarded and the target cells washed with fresh medium. Approximately 9-11 days after the initiation of the experiment, plates designated for cytotoxicity were fixed, stained, and scored for surviving colonies in order to determine plating efficiency. Approximately 30-40 days after the initiation of the experiment, plates were fixed, stained, and scored for the morphologically-transformed phenotype. Under the conditions of this assay, the test substance did not induce cell transformation at any of the concentrations tested.
- *Analysis of Sister Chromatid Exchange (SCE) Frequencies in Peripheral Lymphocytes of Rabbits Exposed Subacutely to [3-Glycidoxypropyltrimethoxysilane] (Allied Corporation Report No. MA-168-81-9; Dow Corning Corporation internal report number 1999-I0000-46219) and Analysis of Sister Chromatid Exchange (SCE) Frequencies in Peripheral Lymphocytes of Rats and Rabbits Exposed via Inhalation to [3-Glycidoxypropyltrimethoxysilane] (Allied Corporation Report No. MA-168-81-10; Dow Corning Corporation internal report number 1982-I0065-4122-06).* Preliminary to the referenced *in vivo* studies that were conducted in 1982, *in vitro* SCE assays using rat and rabbit lymphocytes were performed. The results of these preliminary assays are discussed in the referenced reports on the *in vivo* studies. Blood samples from naïve animals were harvested, fixed, stained, and SCE enumerated in accordance with standard operating procedures. The lymphocytes were exposed for one hour to the test substance at concentrations of 0.05, 0.1, and 0.2 mg/ml. Statistically significant increases in SCE frequencies were present at the 0.10 and 0.20 mg/ml concentrations (both species).
- *Evaluation of [3-Glycidoxypropyltrimethoxysilane] for Its Sensitivity to Detoxifying Enzymes from Mammalian Tissues in the Salmonella Typhimurium Mutagenicity Assay (Allied Corporation Report no. MA-168-81-1; Dow Corning Corporation internal report number 1981-I0065-4122-03).* In a study conducted in 1981, the mutagenicity of the test substance was evaluated in the *Salmonella typhimurium* reverse mutation assay using bacterial strain TA-100 only, which was consistently mutated in previous studies. The objective of this study was to determine if metabolic inactivation by mammalian detoxifying enzymes could reduce or eliminate the genetic activity observed in previous studies. The test material (2.5 mg) was incubated in the presence or absence or increasing concentrations (2.5, 6.25, 12.5, 18.75, 25.0, 50.0, or 125.0 mg) of activating medium prepared from microsomal fractions of rat liver, rat lung, rabbit liver, or rabbit lung. Rat liver and lung activation media (post-mitochondrial supernatants; S-9) were prepared from Aroclor-induced animals. Activating media from rabbits (post-mitochondrial supernatants; S-9) was prepared from uninduced animals. The pre-incubated samples were then tested in the *Salmonella typhimurium* reverse mutation assay using bacterial strain TA-100 only. As the concentration of the S-9 supernatant from rat liver in the pre-incubation mixture was increased, a significant decrease in the mutagenic activity of the test substance was observed. This was also noted when rat lung, rabbit liver, and rabbit lung were the sources of the S-9 supernatant. To confirm that the apparent decrease in mutagenic activity

was the result of enzymatic inactivation, and not the result of non-specific interactions with the proteins, the experiment was repeated using heat-inactivated rabbit S-9 fractions. There was no decrease in mutagenic potential observed when the test material was pre-incubated with heat-inactivated rabbit liver or lung S-9. These results strongly suggest that the reduced mutagenic potential of the test substance after treatment with mammalian tissue homogenates was the result of enzymatic detoxification, and that the mutagenicity of the test substance in the standard Ames mutagenicity assay may not reflect its mutagenic potential in mammalian systems due to the presence of enzymes capable of inactivating the reactive epoxide moiety.

- *Genetic Toxicology Studies of [3-Glycidoxypropyltrimethoxysilane] (Allied Corporation Report No. MA-168-81-12).* This report, written in 1982, provides an overview of the genetic toxicity of the test substance based on the review of numerous *in vitro* and *in vivo* studies. It concludes that the test substance does not pose a significant genetic risk in intact animals.

Genetic Toxicity *In Vivo* (Chromosomal Aberrations)

Test Substance

Identity: 3-Glycidoxypropyltrimethoxysilane (CAS No. 2530-83-8)

Method

Method/Guideline Followed:	The study was conducted in general conformance with OECD Health Effects Test Guideline No. 475 (April 4, 1984).
Type/Test Type:	*In vivo* mouse micronucleus chromosomal aberration
GLP (Y/N):	Yes
Year (study performed):	1982
Species:	Mouse
Strain:	CD-1
Sex:	Male and female
Route of Administration:	Oral via gastric intubation (gavage)
Dose Levels:	0.5, 1.67 and 5.0 g/kg of undiluted test substance
Exposure Period:	Doses were administered on a split-dose schedule at time 0 and at 24 hours
Statistical Methods:	Increases in the frequency of micronucleated cells were compared between the treated and negative control group using the Student T-test. Analysis of the data was made for males only, females only and combined male plus female data.

Remarks Field for Test Conditions

Young adult (7-12 weeks old) mice weighing between 20 and 40 grams were used. There were 10 mice per group (five per sex). The test substance was administered undiluted.

A water-dosed negative control group and a positive control group were also included. The positive control group received triethylemelamine by intraperitoneal injection (1 g/kg). All doses were given using the previously described split schedule. Six hours after the last dose was given, the mice were euthanized using CO_2 and femoral bone marrow smears were prepared. Aspirated bone marrow was transferred to centrifuge tubes (one per mouse) containing fetal calf serum. Following centrifugation, a portion of the resultant pellet was spread on a glass slide and allowed to air dry. The slides were stained in May-Gruenwald solution and Giemsa.

One thousand polychromatic cells per animal were scored. The slides were coded and analyzed blindly with respect to treatment.

Results

All test substance-treated mice survived to the scheduled euthanization. There were no statistically significant increases of the micronucleus frequency in any of the treated groups, relative to the untreated (water) control group. The positive control induced an approximate eight-fold and statistically significant increase of the micronucleus frequency.

The No Observed Adverse Effect Level (NOAEL) for chromosomal aberration was greater than 5 g/kg orally in mice under the conditions of this assay.

Conclusions

Remarks Field with Ability to Identify Source of Comment

The test substance, 3-glycidoxypropyltrimethoxysilane, did not induce chromosome damage in the bone marrow cells of mice following oral administration of a very high dose, i.e., 5 g/kg.

Data Quality

Remarks Field for Data Reliability

Based on a review of the report, the study was judged to be scientifically defensible.

References

Key Study: Dow Corning Corporation internal report number 1982-I0005-1017.

Other

Last changed (administrative field for updating):

Order number for sorting (administrative field):

Supporting Data:

- *Analysis of Sister Chromatid Exchange (SCE) Frequencies in Peripheral Lymphocytes of Rats and Rabbits Exposed via Inhalation [to 3-Glycidoxypropyltrimethoxysilane] (Allied Corporation Report No. MA-168-81-10, Dow Corning Corporation internal report number 1982-I0065-4122-06).* In a study conducted in 1982, the test substance was evaluated *in vivo* for its potential to induce Sister Chromatid Exchanges (SCE) in the lymphocytes of rabbits and rats. Rats (4/group) and rabbits (3/group) were exposed by inhalation to target levels of aerosol of 75, 225, and 750 mg/M^3/day, six

hours per day for nine days. Negative (air) and positive (mitomycin-C, 1 mg/kg on days 0 and 7) controls were included. A repeat study in rabbits using 5/group (negative control, positive control and 225 mg/M^3 only) was also performed. Blood samples were taken before, during and after the exposure period. Mitogen was added to the blood culture to stimulate lymphocytes to divide, BrdU was added and the cultures incubated a defined period of time. Samples were harvested, fixed, stained, and SCE enumerated in accordance with standard operating procedures. Nine 6-hour exposures to the test material aerosol did not result in a significant increase in sister chromatid exchanges in the lymphocytes of rabbits or rats at any of the concentrations tested.

- *Analysis of Sister Chromatid Exchange Frequencies in Peripheral Lymphocytes of Rabbits Exposed Subacutely to [3-Glycidoxypropyltrimethoxysilane] (Allied Corporation Report No. MA-168-81-9, Dow Corning Corporation internal report number 1999-I0000-46219).* In a study conducted in 1982, the test substance was evaluated *in vivo* for its potential to induce sister chromatid exchanges (SCE) in the lymphocytes of rabbits. Male NZW rabbits (2/dose group) weighing approximately 2.5 kg were exposed by intraperitoneal injection (5 d/wk, 2 wk) to the test substance (30 and 100 mg/kg/day). The test substance was diluted in DMSO for administration (30 mg/ml and 125 mg/ml, respectively). Negative (DMSO, 2 ml/dose) and positive (mitomycin-C, 1 mg/kg on days 0 and 7) controls were also included. Blood samples were taken from an ear vein before, during and after the exposure period. Mitogen was added to the blood culture to stimulate lymphocytes to divide, BrdU was added and the cultures incubated a defined period of time. Samples were harvested, fixed, stained, and SCE enumerated in accordance with standard operating procedures. The test substance failed to induce significant increases in sister chromatid exchange frequency in a consistent, dose-related manner at either tested dosage.
- *Genetic Toxicology Studies of [3-Glycidoxypropyltrimethoxysilane] (Allied Corporation Report No. MA-168-81-12).* This report, written in 1982, provides an overview of the genetic toxicity of the test substance based on the review of numerous *in vitro* and *in vivo* studies. It concludes that the test substance does not pose a significant genetic risk in intact animals.

Other Data:

- *Mammalian Erythrocyte Micronucleus Test (Trevira Corporation Project No. C-2102).* In a GLP study conducted in 1998, the test substance was injected intraperitoneally into young adult mice in a micronucleus chromosomal aberration study. There were 10 or 20 mice per group. The test substance was administered as a solution in sterile distilled water. The dosing solutions were allowed to stir for at least 30 minutes, which may have resulted in test substance hydrolysis, prior to use. A water-dosed negative control group and a positive control group were also included. The positive control group received cyclophosphamide by intraperitoneal injection (50 mg/kg). There were 10 mice per sex in the negative control and high test dose (2 g/kg) groups and 5 mice per sex in the low and mid dose test groups (0.5 and 1.0 g/kg) and in the positive control group. Five mice per sex per group were euthanized 24 hours after dosing. The remaining five mice per sex in the negative control and high dose groups were euthanized 48 hours after dosing. Immediately after euthanization, bone marrow smears were prepared. The slides were fixed in methanol, stained in May-Gruenwald solution and Giemsa and permanently mounted. Two thousand polychromatic cells (PCE) per animal were scored for the presence of micronuclei. Micronucleated normochromic erythrocytes were enumerated. The proportion of PCE to total erythrocytes (TE) was also recorded.

  The full complement of mice survived to the scheduled euthanizations. The positive control induced a significant increase in the number and frequency of micronuclei and a 31-35% reduction of the

PCE/TE ratio. Reductions (22-37%) of the PCE/TE ratios were seen in the test substance treated groups at 24 hours after dosing and at 48 hours (59% for males and 45% for females) in the 2.0 g/kg group. The numbers of micronucleated polychromic erythrocytes (MPE) were statistically increased in a dose-response for the three test substance-treated groups at 24 hours and at 48 hours for the 2.0 g/kg group, although much less so than at 24 hours.

The hydrolyzed test substance induced chromosome damage in the bone marrow cells of mice under the conditions of this study. However, the route of administration that was used (intraperitoneal injection) is not considered representative of a realistic human exposure scenario. Previous animal studies (see Key Study and Supporting Data, first bullet, above) by relevant exposure routes (oral, inhalation) using high doses have not shown similar genotoxic effects.

Oral administration of undiluted test substance to mice did not induce erythrocytic chromosomal aberrations. Thus, the test substance is not considered to possess inherent chromosomal aberration induction potential by a relevant route of exposure, nor is it considered to pose a significant genetic risk in intact animals (see Supporting Data, third bullet, above).

Repeat Dose Toxicity

Test Substance

Identity: 3-Glycidoxypropyltrimethoxysilane (CAS No. 2530-83-8)

Method

Method/Guideline Followed:	OECD Health Effects Test Guideline No. 407 (May 12, 1981)
Test Type:	Subacute oral toxicity in rats
GLP (Y/N):	Yes
Year (study performed):	1981
Species:	Rat
Strain:	Sprague-Dawley
Route of Administration:	Oral via gastric intubation (gavage)
Duration of Test:	28 days
Dose Levels:	40, 400 and 1000 mg/kg/day.
Sex:	Male and female
Frequency of Treatment:	Five consecutive days per week for four weeks
Control Group and Treatment:	A negative control group of 20 rats was dosed with water only on the same schedule as the treated groups.
Post Exposure Observation Period:	Not applicable. The rats were observed daily during the treatment period. All rats were euthanized and necropsied upon completion of the treatment period; no recovery or other satellite groups were included.
Statistical Methods:	Statistical comparisons between the control and treated groups were carried out where appropriate. Body weights, food consumption, hematology values, blood chemistry values and absolute and relative organ weights were analyzed by a one-way analysis of variance. Group means were compared to control values using Dunnett's multiple t-test. Where appropriate, a non-parametric analysis of variance by ranks was used to evaluate these parameters. The 95% ($P \leq 0.05$) confidence level was chosen as the criteria of significance.

Remarks Field for Test Conditions

There were 9-11 rats per sex in each group. Young adult rats weighed 260 ± 21 grams (males) and 219 ± 15 grams (females) at initiation of dosing. No vehicle was used; the test substance was administered undiluted. Observation for mortality and clinical condition was performed daily. Individual body weights and food consumption were measured every four days. Hematological (all animals), blood biochemical (all animals) and urine analysis (5/sex/group) studies were carried out at the end of the treatment period. Hematological parameters evaluated were erythrocyte count, hemoglobin level, hematocrit, reticulocyte count, platelet count and total and differential leukocyte counts. Blood chemistry parameters were alkaline phosphatase, glutamic pyruvic transaminase, glutamic oxalacetic transaminase, blood urea nitrogen, lactic dehydrogenase, total protein, total bilirubin, total cholesterol, creatinine, Ca, Na, K, Cl, P, glucose, albumin and globulin. Urinalysis parameters were specific gravity, glucose, bile pigments, ketone bodies, protein, pH, occult blood and bilirubin. All rats received a gross pathological examination that included all major tissues, organs, orifices and the cranial, abdominal and pelvic cavities and their viscera. Fresh organ weights were recorded for liver, brain, kidneys, lungs, heart, spleen, adrenals, testes and ovaries. Paired organs were weighed separately. The following organs/tissues were collected from all rats and preserved in 10% neutral buffered formalin: liver, kidneys, brain, sciatic nerve, mesenteric lymph node, urinary bladder, heart, lungs, gonads, spleen, pituitary, prostrate/uterus, thyroid, parathyroid, adrenals, stomach, small and large intestines, bone, seminal vesicles, epididymides and gross lesions. All of these tissues from the control and high dose groups were examined microscopically.

Results

There were no test substance-related mortalities. One 40 mg/kg/day male and two 1000 mg/kg/day males died during the course of the study. However, necropsy of these rats revealed test substance to be present in the lungs and thus the deaths were associated with dosing trauma. There were no test substance-related effects on clinical condition, behavior, body weight, body weight changes or food consumption, nor were there any test substance-related effects on hematological, blood biochemical or urinalysis parameters; some statistical differences from control values were present in these data, but all values for the treated groups were within normal ranges. No test substance-related organ weights effects or gross or microscopic pathological changes were observed.

Under the conditions of this study, the NOAEL (No Observed Adverse Effect Level) for the test substance was found to be 1000 mg/kg/day or greater when administered orally five days per week for four weeks to male and female rats.

Conclusions

Remarks Field with Ability to Identify Source of Comment

The test substance has a low order of toxicity in rats by repeated oral administration. The NOAEL exceeds current OECD and EPA maximum dose level requirements for studies of this type.

Data Quality

Remarks Field for Data Reliability

Based on a review of the report, the study was judged to be scientifically defensible.

References

Key Study: Dow Corning Corporation internal report number 1981-I0005-900.

Other

Last changed (administrative field for updating):

Order number for sorting (administrative field):

Remarks Field for General Remarks

As our experience and knowledge associated with the issues surrounding the testing of TMSPGE increased, it has become apparent that it is not stable by the oral route. Specifically, TMSPGE readily hydrolyzes to methanol and silanols (Note: methanol is included in the EPA HPV Challenge Program). pH has a significant effect on the rate of hydrolysis, and at pH 4, the hydrolysis is complete within 2.5 minutes. Slight changes in pH affect the rate of hydrolysis, which may result in administration of differing forms of the test article with each dosing. The hydrolysis rate is susceptible to the presence of trace acid and/or base.

A non-GLP study was conducted to examine the fate of TMSPGE following oral (gavage) exposure. Five fasted female Sprague-Dawley rats were dosed with 2000 mg/kg TMSPGE mixed with activated charcoal as a tracer. After 20 or 30 minutes the animals were sacrificed, and the stomachs and gastrointestinal tracts examined for presence of test article. The study was also repeated in the absence of the activated charcoal tracer. In all cases, the hydrolysis product(s) of the test article were found in the stomach contents or in the upper gastrointestinal tract, and was observed to have the consistency of a siloxane gel. In cases where the stomach contents included food, small waxy particles of test article were observed. Both the gel-like substance and waxy particle forms of the hydrolysis products of the test article observed in the stomach and upper gastrointestinal tract support the rapid polymerization of TMSPGE under oral (gavage) conditions, as the test article exists as a clear, water like liquid. In either case, little or no absorption of test article appeared to have occurred. In contrast, there was no liquid present in the stomachs of animals gavaged with an equivalent dose of water and sacrificed after 30 minutes.

The lack of clinical signs of toxicity following acute or repeated dosing is likely related to the hydrolysis of TMSPGE and subsequent polymerization of the hydrolysis products, and thus, the lack of bioavailability. The recognition of the instability of TMSPGE precludes future testing of this material via the oral route.

Development Toxicity/Teratogenicity

Test Substance

Identity: 3-Glycidoxypropyltrimethoxysilane (CAS No. 2530-83-8)

Method

Method/Guideline Followed:	OECD Health Effects Test Guideline No. 414 (May 12, 1981)
GLP (Y/N):	Yes
Year (study performed):	1982
Species:	Rat
Strain:	Sprague-Dawley
Route of Administration:	Oral via gastric intubation (gavage)
Dose Levels:	50, 500 and 1000 mg/kg/day.
Sex:	Female (only)
Exposure Period:	Test substance exposure occurred during the primary period of organogenesis, i.e., gestation days 6-15.
Frequency of Treatment:	Once per day on gestation days 6-15.
Control Group and Treatment:	A negative control group of 20 rats was dosed with water only on the same schedule as the treated groups.
Duration of Test:	The overall duration of the test was approximately three weeks.
Statistical Methods:	Fetal body weights and body measurements, maternal body weights, weights of the maternal livers and uteri and food consumption data were analyzed statistically by a one-way analysis of variance and Dunnett's test (Steel and Torrie, 1960). The Wilcoxon test as modified by Haseman and Hoel (1974) was used to evaluate incidences of fetal resorptions and alterations. Other incidence data were analyzed statistically by the Fischer exact test (Seigel, 1956). The level of significance chosen for all cases was $p < 0.05$.

Remarks Field for Test Conditions

The study used timed-pregnant female Sprague-Dawley rats. The supplier performed breeding of the rats. The rats weighed 265 ± 44 grams at initiation of dosing.

No vehicle was used; the test substance was administered undiluted.

Observation for mortality and clinical condition was performed daily. Maternal body weights and food consumption were recorded on gestation days 6, 10, 15 and 20. Individual animal doses were adjusted for body weight on gestation days 6, 10 and 15. On gestation day 20, the rats were euthanized and laparohysterectomies were performed. Maternal liver weights and gravid uterine weights (including the ovaries) were recorded. The number and position of live, dead and resorbed fetuses were recorded, as was the number of corpora lutea. All fetuses were weighed, measured (crown-rump length), sexed and examined for external alterations and cleft palate. One-third of the fetuses from each litter were randomly selected for immediate examination by dissection under a stereo microscope for soft tissue alterations (Staples, 1974). The head of each fetus examined for soft tissue alterations was placed in Bouin's fixative and subsequently examined by the razor sectioning technique (Wilson, 1965). All of the fetuses in each litter were eviscerated, placed in 95% ethanol, subsequently cleared with potassium hydroxide and stained with Alizarin red-S (Dawson, 1926) to permit examination for skeletal alterations.

Results

There were no test substance-related mortalities. One rat (subsequently replaced) in the 50 mg/kg/day group died as the result of dosing trauma. There were no test substance-related effects on clinical condition, behavior, body weight, body weight gain or food consumption. No effects on liver or gravid uterine weight were observed. No effects on the number of implantation sites or corpora lutea per dam were observed. The incidence of pregnancy was not affected by treatment with the test substance; all rats were confirmed to be pregnant at the gestation day 20 laparohysterectomies. No adverse effects on the number of live fetuses per litter, mean litter size, sex ratio, fetal body weight or crown-rump length were observed. The incidence of fetal resorptions was not altered by test substance administration. No external, visceral or skeletal alterations were observed among test substance-treated rats at an incidence that was statistically different from the control group. When considered collectively, the incidence of total major malformations observed in the external, soft tissue or skeletal examinations was not significantly different among the treated groups as compared to the control group. No major malformations were observed among litters of rats that received either 500 or 1000 mg/kg/day of the test substance. The sporadic variations and malformations seen occurred at an incidence comparable to a historical control incidence for Sprague-Dawley rats reported in the literature.

Under the conditions of this study, the NOAEL (No Observed Adverse Effect Level) of the test substance for embryotoxicity, developmental toxicity and maternal toxicity was found to be 1000 mg/kg/day or greater when administered orally on gestation days 6-15 to rats.

Conclusions

Remarks Field with the Ability to Identify Source of Comment

The test substance exhibited no adverse effects on the maternal animals or the developing unborn. The NOAEL for maternal and developmental toxicity exceeds current OECD and EPA maximum dose level requirements for studies of this type.

Data Quality

Remarks Field for Data Reliability

Based on a review of the report, the study was judged to be scientifically defensible.

References

Key Study: Dow Corning Corporation internal report number 1983-I0005-963.

Other

Last changed (administrative field for updating):

Order number for sorting (administrative field):

Remarks Field for General Remarks

As our experience and knowledge associated with the issues surrounding the testing of TMSPGE increased, it has become apparent that it is not stable by the oral route. Specifically, TMSPGE readily hydrolyzes to methanol and silanols (Note: methanol is included in the EPA HPV Challenge Program). pH has a significant effect on the rate of hydrolysis, and at pH 4, the hydrolysis is complete within 2.5 minutes. Slight changes in pH affect the rate of hydrolysis, which may result in administration of differing forms of the test article with each dosing. The hydrolysis rate is susceptible to the presence of trace acid and/or base.

A non-GLP study was conducted to examine the fate of TMSPGE following oral (gavage) exposure. Five fasted female Sprague-Dawley rats were dosed with 2000 mg/kg TMSPGE mixed with activated charcoal as a tracer. After 20 or 30 minutes the animals were sacrificed, and the stomachs and gastrointestinal tracts examined for presence of test article. The study was also repeated in the absence of the activated charcoal tracer. In all cases, the hydrolysis product(s) of the test article were found in the stomach contents or in the upper gastrointestinal tract, and was observed to have the consistency of a siloxane gel. In cases where the stomach contents included food, small waxy particles of test article were observed. Both the gel-like substance and waxy particle forms of the hydrolysis products of the test article observed in the stomach and upper gastrointestinal tract support the rapid polymerization of TMSPGE under oral (gavage) conditions, as the test article exists as a clear, water like liquid. In either case, little or no absorption of test article appeared to have occurred. In contrast, there was no liquid present in the stomachs of animals gavaged with an equivalent dose of water and sacrificed after 30 minutes.

The lack of clinical signs of toxicity following acute or repeated dosing is likely related to the hydrolysis of TMSPGE and subsequent polymerization of the hydrolysis products, and thus, the lack of bioavailability. The recognition of the instability of TMSPGE precludes future testing of this material via the oral route.